PATENT APPLICATION
Attorney Docket No. 05569.0011.DVUS05
(Previously 213839-00022)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Winter, *et al.*
App. No.:	09/726,650
Filing Date:	November 28, 2000
Title:	METHOD FOR TAPPING IMMUNOLOGICAL REPERTOIRE
Art Unit:	1636
Examiner:	J. S. Ketter

CERTIFICATE OF MAILING

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APPEAL BRIEF UNDER 37 CFR § 1.192(c)

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Sir:

Attorney for applicants submit herewith the Appeal Brief for the above-referenced application, for which a Notice of Appeal was filed on December 10, 2003 (postcard stamped received December 15, 2003). It is requested that the fee for filing an appeal brief in the amount of $330 pursuant to 37 CFR 1.17(b) be charged to our Deposit Account No. 08-3038. A Request for Extension of Time is submitted herewith requesting an extension of time within the fourth month in the amount of $1,480. If proper payment is not enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 08-3038.

A. Real Party in Interest

This application is assigned to Scripps Research Institute, La Jolla, California; Medical Research Council, London, England; and Stratagene, La Jolla, California.

B. Related Appeals and Interferences

Applicants bring to the attention of the Examiner that co-pending application 09/726,646, filed November 28, 2000, is currently under appeal.

C. Status of Claims

Claims 22-29 are currently pending in the application and are finally rejected in the Office Action of September 10, 2003 under 35 USC § 102(e) and 35 USC § 112, first and second paragraphs. Applicants appeal from the primary Examiner's decision to reject claims 22-29 for the reasons explained below. Claims 22-29 are set out in Appendix A.

D. Status of Amendments

There was no amendment filed subsequent to final rejection.

E. Summary of the Invention

Antibodies (immunoglobulins) are proteins produced in the body that are capable of binding specifically to certain ligands, such as antigens, enzyme substrates, and others. Certain antibodies also have catalytic activity. Figure 1 of attached Appendix B of the present specification is a schematic diagram of an immunoglobulin molecule showing its principal structural features including *inter alia,* variable heavy chain and variable light chain which make up the ligand binding portion of the molecule. Antibody molecules are coded for in the body by a multiplicity of genes which, when rearranged in the body, give rise to a large number of different antibodies each of which is unique.

The present invention arises in part from the discovery that genes encoding the variable regions of immunoglobulin molecules share certain conserved sequences amongst one another. The presence of these conserved sequences allow the preparation of immunoglobulin gene libraries which comprise a plurality of different immunoglobulin genes and/or genes which encode various parts of an immunoglobulin molecule including but not limited to variable heavy chain genes (V_H genes) and variable light chain genes (V_L genes).

In particular, the present invention is directed to a V_H and V_L polypeptide which, when paired with one another, have a catalytic activity and which is prepared by a recited process. The combination of V_L and V_H may be in the form of a whole antibody or a fragment of an antibody.

The process for preparing the polypeptide comprises synthesizing a gene library encoding a plurality of different V_H and V_L coding sequences. Prior to the applicants' discovery, immunoglobulin genes were usually isolated individually; the discovery of conserved regions allows those of skill in the art to synthesize libraries of genes encoding antibody light and heavy chain variable regions with a diverse range of specificites.

More specifically, the gene library is synthesized by preparing a first polynucleotide composition wherein at least a portion of the polynucleotides in the composition comprise a plurality of different V_H coding sequences and preparing a second polynucleotide composition wherein at least a portion of the polynucleotide sequences in the composition comprise a plurality

of different V_L coding sequences. The V_H and V_L coding sequences are then amplified, for example, using the polymerase chain reaction in which the primers represent conserved sequences that flank the V_H and V_L coding sequences in the gene library. The amplified V_H and V_L coding sequences are then joined in operable combination with expression vectors so as to allow the expression of the V_H and V_L coding sequence from each vector, thereby forming a diverse library.

The V_L and V_H coding sequences may be on the same expression vector or on separate expression vectors. Catalytic antibodies and their encoding polynucleotides from the gene library are selected from the library by binding to a predetermined substrate.

F. Issues

The issues involved in this appeal are:

1. Whether the U.S.P.T.O. was erroneous in finding that the subject matter of claims are anticipated under 35 U.S.C. § 102(e) over alleged prior art that fails to disclose all of the elements of the rejected claims; and

2. Whether the U.S.P.T.O. was erroneous in rejecting claims 22-29 by requiring that the specification provide precise structures in order to meet the written description requirement of 35 USC § 112, first paragraph, despite a detailed description of structural and functional features of the claimed polypeptides.

3. Whether the U.S.P.T.O. was erroneous in rejecting claims 22-29 under 35 U.S.C. § 112, second paragraph, as allegedly " failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention in view of the use of the phrase "A V_H and V_L polypeptide... ."

G. Grouping of Claims

Claims 22-29 stand or fall together on each ground of rejection.

H. Argument

A. The Cited Art Fails to Describe Every Element of the Claimed Invention and Cannot Anticipate the Present Claims and Therefore the Rejections Under 35 USC § 102(e) are Erroneous and Should Be Withdrawn.

The Examiner has erroneously rejected claims 22-29 under 35 U.S.C. § 102(e) as allegedly being anticipated by Iverson *et al.* and Kim *et al.* and Schochetman *et al.* for reasons set out in Paper 19, mailed on 14 March 2003. As a first matter, the applicants wish to point out that to their knowledge no Paper 19, mailed 14 March 2003, exists in this case. However, we believe that this was an inadvertent error on the part of the Examiner in that the reasons for rejection were actually set out in Paper No. 18 mailed 11 February 2003. Clarification is requested.

The applicants respectfully submit that the rejections are improper in that neither reference teaches every element of the presently claimed invention, that is, they fail to disclose the process limitations of the instant product-by-process claims and thus, as a matter of law, cannot properly anticipate the invention.

It is well settled law that in order to anticipate a claim a prior art reference must disclose, either expressly or inherently, all of the limitations of the claims. *Transclear Corp. v. Bridgewood Services*, 290 F.3d 1364, 62 USPQ2d 1865 (Fed.Cir. 2002). See also *Gechter v. Davidson*, 116 F.3d 1454, 1456, 43 USPQ2d 1030, 1032 (Fed.Cir. 1997). ("Under 35 U.S.C. § 102, every limitation of a claim must identically appear in a single prior art reference for it to anticipate the claims"); *United States Filter Corp. v. Ionics, Inc.*, 68 F.Supp.2d 48, 55 USPQ2d 1071, 1077 (D.Mass. 1999), ("If a prior art reference lacks any claimed element, then as a matter of law, a decision maker (whether in the Patent Office or in a Court) cannot find any anticipation.") Indeed, this principal of law is in accordance with the findings of many courts that in order to infringe a product-by-process claim, the alleged infringer must practice the claimed process and that a similar or the same product made by a different process does not infringe a product-by-process claim. See, *e.g., Atlantic Thermoplastics Co., Inc. v. Faytex Corp.*, 970 F.2d 834, 846 (Fed. Cir. 1992) ("Thus, process terms in product-by-process claims serve as limitations

in determining infringement.") A common principal uniting these series of cases is that all of the elements of a claim must be considered under both the anticipation and infringement analysis. Yet in the present case, the Examiner continues to studiously ignore explicit claim elements in finding that the present claims are anticipated by the Iverson *et al.*, Kim *et al.* and Schochetman *et al.*, each of which fail to teach the process elements presently claimed.

The applicants respectfully submit that this combination of features is novel, distinct and defines a product, specifically, a catalytic antibody or antibody fragment produced by the recited method and selected for its ability to bind a particular ligand/antigen and catalyzes an enzymatic reaction. Iverson *et al.* discloses catalytic antibodies produced by way of a hybridoma while Kim *et al.* teaches the production of a catalytic antibody by immunization of an animal. Schochetman also teaches a mouse monoclonal antibody made using hybridoma technology.

Among the claim elements not taught by either cited reference are:

(a) producing a V_H and V_L-coding genetic library, by a method comprising the steps of:
  (i) adding a first primer, wherein said first primer is capable of hybridizing to a first conserved nucleotide sequence substantially adjacent to a plurality of V_H-coding regions, and said coding sequences are present in a polynucleotide containing composition that comprises a plurality of different V_H and V_L coding sequences;
  (ii) adding a second primer to said nucleotide containing composition, wherein said second primer is capable of hybridizing to a second conserved nucleotide sequence substantially adjacent to a plurality of different V_H-coding regions;
  (iii) adding a third primer, wherein said third primer is capable of hybridizing to a third conserved nucleotide sequence substantially adjacent to a plurality of V_L-coding regions;
  (iv) adding a fourth primer to said polynucleotide containing composition, wherein said fourth primer is capable of hybridizing to a fourth conserved nucleotide sequence substantially adjacent to a plurality V_L-coding regions;
  (v) amplifying said V_H coding sequences and said V_L coding sequences;
(b) joining in operable combination said amplified V_H and V_L-coding sequences with expression vectors so as to be able to express V_H and V_L-coding sequence from said vectors, whereby a diverse library is formed;
(c) selecting and isolating from said diverse library expression vector

capable of producing V_H or V_L polypeptides which in combination have said catalytic activity;

(d) transforming a host cell with said expression vectors; and

(e) isolating a V_H and V_L polypeptide encoded by said vector from said host cell.

Because, neither Iverson *et al.* nor Kim *et al.* nor Schochetman *et al.* disclose all of the elements claimed in the instant invention, the applicants respectfully submit that the rejections under 35 U.S.C. § 102(e) are as a matter of law, improper and should be withdrawn. (See, *e g., Transclear Corp., supra.*; *Gechter, supra*)

B. The Rejections of Claims 22-29 Based On An Alleged Lack of Sufficient Written Description Under 35 USC §112, First Paragraph is Erroneous and Should Be Withdrawn

Despite the detailed description of the structure, sequence association constants and function of the antibodies and antibody fragments encompassed by the present claims provided by the specification, the Examiner has improperly rejected claims 22-29 as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to a person of ordinary skill in the art, at the time the invention was filed, that the inventor had possession of the claimed invention. More precisely, the Examiner improperly requires the applicants to provide precise structures of members of the genus of catalytic antibodies or antibodies fragments. The Applicants respectfully submit that the law does not require the elucidation of precise structures of species within a genus and to do so now is improper.

The purpose of 35 USC § 112, first paragraph, is to ensure that the inventor had possession, as of the filing date of the application relied on of the subject matter claimed. In *Re Alton,* 76 F.3d 1168, 1172, 37 USPQ2d 1578, 1581 (Fed. Cir. 1996). How the specification accomplishes this is not material. *Id.* The written description requirement is satisfied if a skilled artisan would have understood the inventor to be in possession of the claimed invention. "Although [the applicant] does not have to describe exactly the subject matter claimed, the description must clearly allow persons of ordinary skill in the art that [he or she] inventors invented what is claimed". *In re Gosteli,* 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed.

Cir. 1989) (citation omitted). "[T]he test for sufficiency of support in patent application is whether the disclosure of the application relied upon reasonably conveys to the artisan that the inventor had possession of the later claimed subject matter". *Id,* citing *Ralston Purina Co. v. Far-Mar-Co. Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1989), quoting, *In re Kaslow* 707 F.2d 1366, 1375, 217 USPQ 1059, 1096 (Fed. Cir. 1983).

Written description may be satisfied through disclosure of relevant identifying characteristics, *i.e.*, structure, other physical and/or chemical characteristics, functional characteristics when correlated with a known or disclosed correlation between function and structure or some combination of such characteristics. See, Guidelines for Examination of Patents Applications Under 35 USC § 112, ¶1, *Written Description Requirement*, 66 Fed. Reg. 1099, 1106.

Other examples of relevant identifying characteristics include a sequence, a structure, binding affinity, binding specificity, molecular weight and length. Although structural formulas provide a convenient method of demonstrating possession of specific molecules, other identifying characteristics can demonstrate the requisite possession. For example, unique cleavage by particular enzymes, isoelectric points of fragments, detailed restriction enzyme maps, a comparison of enzymatic activities, or antibody cross reactivity may be sufficient to show possession of the claimed invention to one of skill in the art. *See Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997) ('written description' requirement may be satisfied by using 'such descriptive means as words, structures, figures, diagrams, formulas, etc. that fully set for the claimed invention').

The present specification provides abundant description of the claimed subject matter in terms of structural and functional characteristics and thus meets the written description requirement of 35 U.S.C. § 112, first paragraph. As discussed above, the present invention is directed to catalytic antibodies or antibody fragment produced by the recited methods. The structure of immunoglobulin (antibody) molecules and parts thereof are described *inter alia* in the specification by the molecule types "IgD, IgG, IgA, IgM and IgE." *(Specification, page 15, line 35, - page 16, line 1)*. Their structures are further described as comprising "... two heavy (H) and light (L) chains with both a variable (V) and constant (C) region present on each chain."

(Specification, page 16, lines 1-4). Further, the applicants submit that the structure and function of such molecules are well known by persons of ordinary skill in the art as being capable of binding to a wide variety of ligands such as antigens or enzyme substrates. The specification also describes additional structural features of the molecules stating that,

> "[S]everal different regions of an immunoglobulin contain conserved sequences useful for isolating an immunoglobulin repertoire. Extensive amino acid and nucleic acid sequence data displaying exemplary conserved sequences is compiled for immunoglobulin molecules by Kabat et al., in Sequences of Proteins of Immunological Interest, National Institutes of Health, Bethesda MD 1987.
>
> "The C region of the H chain defines the particular immunoglobulin type. Therefore the selection of conserved sequences as defined herein from the C region of the H chain results in the preparation of a repertoire of immunoglobulin genes having members of the immunoglobulin type of the selected C region."
>
> "The V region of the H or L chain typically comprises four framework (FR) regions each containing relatively lower degrees of variability that includes lengths of conserved sequences. The use of conserved sequences from the FR1 and FR4 (J region) framework regions of the V_H chain is a preferred exemplary embodiment and is described herein in the Examples. Framework regions are typically conserved across several or all immunoglobulin types and thus conserved sequences contained therein are particularly suited for preparing repertoires having several immunoglobulin types."
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> *Specification, page 16, lines 4-31.*

The specification also delineates examples of the size ranges of the V_H and V_L polypeptide chains stating that:

> "The individual V_H and V_L polypeptides will generally have fewer than 125 amino acid residues, more usually fewer than about 120 amino acid residues, while normally having greater than 60 amino acid residues, usually greater than about 95 amino acid residues, more usually greater than about 100 amino acid residues. Preferably, the V_H will be from about 110 to about 125 amino acid residues in length while V_L will be from about 95 to about 115 amino acid residues in length.
>
> The amino acid residue sequences will vary widely, depending upon the particular idiotype involved. Usually, there will be at least two cysteines

separated by from about 60 to 75 amino acid residues and joined by a disulfide bond."

Specification at page 21, line 26, through page 22, line 5.

The specification also describes examples of association constants characteristic of the catalytic antibodies (also referred to in the specification as receptors) according to the present invention stating:

> "the subject catalytic receptors have an association constant for the preselected substrates generally greater than 10^5M^{-1} or 10^6M^{-1} and preferably greater than 10^7M^{-1}.

Specification at page 28, lines 10-18.

Examples of sequences which constitute part of and are used in producing catalytic antibodies or antibody fragments according to the present invention are illustrated in Table 1, Table 2, Table 3, and Table 4 and in Figures 3 and 5.

Because the specification describes the catalytic antibodies or antibody fragment of the present invention by *inter alia* how they are made, by certain structural features, by the sequence of certain parts of the catalytic antibodies and by association constants, the applicants submit that the specification fully satisfies the written description requirement of 35 USC § 112, first paragraph and, therefore, the rejection should be withdrawn.

C. The Rejections Under 35 U.S.C. § 112, Second Paragraph, and Erroneous and Should Be Withdrawn

The Examiner has maintained the rejections under 35 U.S.C. § 112, second paragraph, taking issue with the applicant's statement in response to the last office action wherein the applicant stated that "physical attachment of V_H and V_L is not required" which the Examiner alleges is confusing. The applicant respectfully submits that the claim is not confusing in that it simply requires a V_H and a V_L polypeptide which when together, whether linked physically or simply in close enough juxtaposition allows the formation of a binding site for a substrate.

The light and heavy chains of antibodies, when produced by the body, are produced as

two separate polypeptides. In a typical antibody of the IgG class, two copies of each chain are assembled into a whole antibody. The chains are normally cross-linked to each other by disulfide bonds though remain as separate polypeptides (see Figure 1 of the present application). However, various antibody fragments are known in the art which, while retaining the light and heavy chain variable regions, do not retain the complete structure of a natural antibody. Such fragments include but are not limited to Fv fragments (non-covalently associated heavy and light chain variable regions) and Fab fragments. Both types of fragments are discussed in the instant specification (see, *e.g., Specification at page 20, line 19, through page 21, lines 35*). As taught in the instant application, "[i]n some situations, it is desirable to provide for covalent cross linking of the VH and VL polypeptides, which can be accomplished by providing cysteine residues at the carboxyl termini." (*Specification at page 22, lines 13-16*) Thus, the applicants fully described and contemplated both linked and unlinked VH and VL domains which can be in combination with on another. The precise format (linked or unlinked) is neither an essential feature of the invention nor one which is necessary for delimiting the claims over the prior art.

For that reason, we believe that the claims fully meet the requirement of 35 U.S.C. § 112, second paragraph, and, therefore, that the rejections should be withdrawn.

Conclusion

The Applicants respectfully submit that claims 22-29 cannot be properly anticipated by prior art because the prior art fails to disclose either explicitly or inherently all of the elements of the claims and therefore that the rejections under 35 USC § 102 are erroneous and should be withdrawn.

The Applicants also respectfully submit that the specification provides sufficient written description within its four corners by way *inter alia* of specific structural information, conserved sequences useful in preparing catalytic antibodies and which ultimately make up certain regions of the catalytic antibodies produced by the process of the present invention according to the present invention therefore the rejections under 35 USC § 112, first paragraph, are erroneous and should be withdrawn.

Finally, the Applicants submit that the rejections under 35 U.S.C. § 112, second paragraph, are erroneous and should be withdrawn in that the claims particularly point out and distinctly claim the subject matter which the Applicants regard as their invention.

Respectfully submitted,

HOWREY SIMON ARNOLD & WHITE LLP

November 8, 2004
(Date)

By: _____
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I. Appendix A

Appendix A contains Claims 22-29 presented for review to the Board of Appeals and Interferences.

22. A V_H and V_L polypeptide having in combination with one another a catalytic activity isolated by the method comprising the steps of:

(a) synthesizing a V_H and a V_L-coding gene library containing a plurality of different V_H and V_L -coding DNA sequences by a method comprising the steps of:

(i) preparing a first polynucleotide containing composition, wherein at least a portion of the polynucleotides in said composition comprise a plurality of different V_H-coding sequences;

(ii) preparing a second polynucleotide containing composition, wherein at least a portion of the polynucleotides in said composition comprise a plurality of different V_L-coding sequences;

(iii) amplifying a plurality of V_H and V_L-coding sequences in said respective polynucleotide containing compositions;

(iv) joining in operable combination, V_H and V_L-coding sequences from said V_H and V_L-coding gene library with expression vectors so as to be able to express a V_H and V_L-coding sequence from each vector, whereby a diverse library is formed;

(b) selecting and isolating from said diverse library at least one expression vector capable of producing V_H and V_L polypeptide having in combination with one another catalytic activity;

(c) transforming a host cell with said expression vector; and

(d) isolating a V_H and V_L polypeptide encoded by said vector from said host cell.

23. The V_H and V_L polypeptide of claim 22 wherein said V_H and V_L coding sequences from said V_H and V_L coding library are joined with separate expression vectors.

24. A V_H and V_L polypeptide having in combination with one another a catalytic activity isolated by a method comprising the steps of:

(a) preparing a first polynucleotide containing composition, wherein a portion of the polynucleotides in said composition comprise a plurality of different V_H-coding sequences;

(b) preparing a second polynucleotide containing composition, wherein a portion of the polynucleotides in said composition comprise a plurality of different V_L-coding sequences;

(c) amplifying a plurality of V_H and V_L-coding sequences from said first and said second polynucleotide containing compositions, respectively, by a method of amplification comprising the step of adding primers capable of hybridizing upstream and downstream from a plurality of said V_H coding sequences and adding primers capable of hybridizing upstream and downstream from a plurality of said V_L coding sequences, under conditions permitting hybridization to occur, whereby a plurality of different amplified V_H and a plurality of different amplified V_L coding sequences are produced;

(d) joining in operable combination, said amplified V_H and V_L-coding sequences with expression vectors so as to be able to express a V_H and V_L-coding sequence from each vector, whereby a diverse library is formed;

(e) selecting and isolating from said diverse library at least one expression vector capable of producing a V_H and V_L polypeptide which in combination with one another have said catalytic activity,

(f) transforming a host cell with said expression vector; and

(g) isolating a V_H and V_L polypeptide encoded by said vector from said host cell.

25. The V_H and V_L polypeptide of claim 24 wherein said amplified V_H and said amplified V_L coding sequences are joined with separate expression vectors.

26. A V_H and V_L polypeptide having in combination with one another a catalytic activity isolated by the method comprising the steps of:

(a) producing a V_H and V_L-coding genetic library, by a method comprising the steps of:

(i) adding a first primer, wherein said first primer is capable of hybridizing to a first conserved nucleotide sequence substantially adjacent to a plurality of V_H-coding regions, and said coding sequences are present in a polynucleotide containing composition that comprises a plurality of different V_H and V_L coding sequences;

(ii) adding a second primer to said nucleotide containing composition, wherein said second primer is capable of hybridizing to a second conserved nucleotide sequence substantially adjacent to a plurality of different V_H-coding regions;

(iii) adding a third primer, wherein said third primer is capable of hybridizing to a third conserved nucleotide sequence substantially adjacent to a plurality of V_L-coding regions;

(iv) adding a fourth primer to said polynucleotide containing composition, wherein said fourth primer is capable of hybridizing to a fourth conserved nucleotide sequence substantially adjacent to a plurality V_L-coding regions;

(v) amplifying said V_H coding sequences and said V_L coding sequences;

(b) joining in operable combination said amplified V_H and V_L-coding sequences with expression vectors so as to be able to express V_H and V_L-coding sequence from said vectors, whereby a diverse library is formed;

(c) selecting and isolating from said diverse library expression vector capable of producing V_H or V_L polypeptides which in combination have said catalytic activity;

(d) transforming a host cell with said expression vectors; and

(e) isolating a V_H and V_L polypeptide encoded by said vector from said host cell.

27. The V_H and V_L polypeptide of claim 26 wherein said amplified V_H and V_L coding sequences are joined into separate expression vectors.

28. The V_H and V_L polypeptides of any of claims 22-27 wherein said V_H and V_L polypeptides comprise an Fab.

29. The V_H and V_L polypeptides and of any claims 22-27 wherein said V_H and V_L polypeptides comprise a whole antibody.

Appendix B

U.S. Patent No. 6,291,158